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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,688	03/22/2001	Katherine A. High	CHOP-0026	5212

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/816,688	HIGH ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,13-37,41-49 and 56-84* is/are pending in the application.

4a) Of the above claim(s) *33,36,37,42-49 and 56-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13-32,34,35,41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of species (Factor VII) in the reply filed on 3/11/08 is acknowledged. The traversal is on the ground(s) that there is no burden on the examiner to search both species of modified Factors VII and IX. This is not found persuasive because each species has mutually exclusive characteristics (Each coagulation factor has a different structure and is involved in a different part of the coagulation pathway). A search for Factor VII might not overlap with a search for Factor IX.

The requirement is still deemed proper and is therefore made FINAL.

Claim 64-84 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/11/08.

Claims 33, 36, 37, 42-49, and 56-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and adenovirus, parvovirus, papilloma virus, reovirus, rotavirus and herpes virus in claim 31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/7/06.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or

more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/191,331, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Instant claims 1, 2, 13-32, 34, 35, and 41: There is no written support for SEQ ID NO: 1 in '331. Thus, SEQ ID NO: 1 only enjoys priority to PCT/US01/09355 filed on 3/22/01.

Claim Objections

Claim 34 is objected to because of the following informalities: the claim embraces a non-elected invention (polypeptide). Appropriate correction is required.

Applicant's arguments filed 7/24/07 have been fully considered but they are not persuasive.

In response to applicant's argument that claims 33 and 34 should be rejoined with the elected invention because if claim 1 is allowed then claims 33 and 34 would be allowable, the argument is not found persuasive because of the election/restriction of record. The applicant

elected nucleic acid not polypeptide without traverse. Thus, the assertion by applicant that it would not be an undue burden on the examiner to search claims 33, 34, and 81 is moot because the applicant should have made the argument (with traverse) in response to the election/restriction mailed on 1/12/06.

Claim 1 is objected to because of the following informalities: the term Arg-Lys-Arg-Arg-Lys-Arg (SEQ ID NO: 1), it is not apparent if SEQ ID NO: 1 is an example of the amino acid sequence or is the sequence identifier for the amino acid sequence. Suggest amending the term to as set forth in SEQ ID NO: 1. Appropriate correction is required.

Claim 29 is objected to because of the following informalities: the claim is directed to a composition further comprising a vector (that does not comprise the composition or the recombinant polynucleotide, wherein it appears (in view of the specification) that the vector should contain the recombinant polynucleotide). Suggest amending the claim to read on the vector comprising either composition or the recombinant polynucleotide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The functional limitation in claims 1 and 16-18 (when expressed in an animal cell and secreted in active form) does not have patentable under a prior art rejection teaching a product with the same structure. See MPEP 2112.01 and 2122.

The limitation "wherein the animal cell is mammalian" in claim 15 and "wherein the mammalian cell is human" in claim 16 does not have patentable under a prior art rejection. See MPEP 2112.01 and 2122.

The limitation "instructions for expressing the modified blood clotting factor in vitro, ex vivo, or in vivo" in claim 35 does not have patentable under a prior art rejection. See MPEP 2112.01 (III) and 2122.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best,

Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claims 1, 2, 13-25, 29-32, 34, 35, and 41, are rejected under 35 U.S.C. 103(a) as being unpatentable over Scaria et al. (US 20030229036) taken with Wolf (US 5,795,863).

Scaria teaches viral vectors (e.g., AAV) comprising a promoter operably linked to a nucleic acid encoding a modified Factor VII comprising a PACE/furin cleavage site replacing the activation cleavage site of Factor VII and a pharmaceutical acceptable carrier (pages 1-11). The vector encodes a modified version of Factor VII such that it leads to generation of (or can be converted to) activated Factor VII in vivo (page 3). Scaria teaches that activation of Factor VII to Factor VIIa involves proteolytic cleavage at a single bond between arginine 152 and isoleucine 153 (page 2) resulting in a heavy and light chain. Factor VII can be from any mammalian source, including human (page 4). The Factor VII can have one or more conservative amino acids (page 4). However, Scaria does not specifically teach the PACE cleavage site comprises SEQ ID NO: 1.

However, at the time the invention was made, Wolf teaches a coagulation factor comprising a PACE cleavage site comprising SEQ ID NO: 1 (columns 31-32).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf, namely to produce a vector encoding a Factor VII polypeptide having a proteolytic cleavage site comprising SEQ ID NO: 1. One of ordinary skill in the art would have been motivated to combine the teaching to provide an active amount of Factor VII. "The combination of familiar elements according to

known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf, namely to insert the proteolytic cleavage site is introduced between 152 and 153 of Factor VII. One of ordinary skill in the art would have been motivated to combine the teaching to substitute the native cleavage site with the PACE cleavage site provide an active amount of Factor VII. See ***KSR v. Teleflex***.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf, namely to produce the composition comprising a viral vector selected from an adenovirus and retrovirus. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently express Factor VII in a liver cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 1, 2, 13-32, 34, 35, and 41 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scaria et al. taken with Wolf as applied to claims 1, 2, 13-25, 29-35, and 41 above, and further in view of Amalfitano et al. (US 6,328,958).

Scaria taken with Wolf do not specifically teach using an EF-1-alpha promoter in the composition.

However, at the time the invention was made, Amalfitano teaches a heterologous nucleotide sequence (e.g., clotting factor) operatively associated with a cytomegalovirus (CMV) major immediate-early promoter, an albumin promoter, an Elongation Factor 1-.alpha. (EF1-.alpha.) promoter, a P.gamma.K promoter, a MFG promoter, or a Rous sarcoma virus promoter. See columns 19-20.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf in further view of Amalfitano, namely to produce the composition comprising an EF1-alpha promoter. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently express Factor VII in a cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 1, 24, and 28 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 24, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scaria et al. taken with Wolf as applied to claims 1, 2, 13-25, 29-35, and 41 above, and further in view of Kochanek (US 5,981,225).

Scaria taken with Wolf do not specifically teach using a skeletal muscle actin or muscle creatine kinase (MCK) promoter in the composition.

However, at the time the invention was made, the use of the MCK promoter will lead to tissue specific expression of a foreign gene (column 13).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Scaria taken with Wolf in further view of Kochanek, namely to produce the composition comprising a skeletal muscle actin or muscle creatine kinase promoter. One of ordinary skill in the art would have been motivated to combine the teaching to selectively express Factor VII in a desired cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 1, 24, 26, and 27 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 2, 13-25, 29-32, 34, 35, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf (US 5,795,863) taken with Nicolaisen (US 5,580,560) in further view of Miller et al (US 6,924,365). Wolf teaches a modified coagulation protein comprising the sequence RKRRKR. See columns 31-32. However, Wolf does not specifically teach Factor VII having the proteolytic cleavage site.

However, at the time the invention was made, Nicolaisen teaches that the cDNA coding for Factor VII has been characterized (columns 1-2). The analysis teaches that cleavage of a single peptide bond between arginine 152 and isoleucine 153 converts Factor VII to Factor VIIa. Nicolaisen teaches producing the protein in a cell using an expression vector comprising the nucleic acid (columns 5-6 and 10).

In addition, at the time the invention was made, Miller teaches a nucleic acid sequence that directs synthesize of an optimized message which encodes a coagulation factor protein

having a recognition site for an intracellular protease of the PACE/furin class, e.g., X-Arg-X-X-Arg (columns 5-6 and 20). Miller teaches that viral vectors (adenoviruses, aav, retroviruses) were well known to one of ordinary skill in the art for delivering a nucleic acid to a cell (column 22).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wolf taken with Nicolaisen in further view of Miller, namely to produce a composition comprising a nucleic acid encoding a modified Factor VII having the proteolytic cleavage site as set forth in SEQ ID NO: 1. One of ordinary skill in the art would have been motivated to combine the teaching to produce Factor VII in cells as an optimized message as taught by Miller. See ***KSR v. Teleflex***. Also see In re O 'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wolf taken with Nicolaisen in further view of Miller, namely to produce a nucleic acid encoding factor VII analogue with a modified cleavage site between arginine 152 and isoleucine 153. One of ordinary skill in the art would have been motivated to combine the teaching because the active cleavage site of Factor VII is between these two amino acids. See ***KSR v. Teleflex***.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wolf taken with Nicolaisen in further view of Miller, namely to produce a vector comprising the nucleic acid encoding factor VII analogue with a modified cleavage site. One of ordinary skill in the art would have been motivated to combine the teaching to express the nucleic acid in a cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/24/07 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The totality of the prior makes the claimed invention obvious not Wolf alone. If it was Wolf alone, then the rejection would have been under 102 instead of 103.

Applicant's argues that the teaching of Nicolaisen et al. is directed to modifying Factor VII in order to improve stability, increase half life and slow clearance of the protein from the blood and not introducing RKRRKR into Factor VII would improve stability, increase half life or slow clearance of the protein from the blood. Applicant further argues that Nicolaisen et al. describe modifying a large number of Factor VII residues but failed to suggest modifying amino acids 152 or 153 of Factor VII, let alone introducing a proteolytic cleavage site into Factor VII.

Applicant's argument is acknowledged and is not found persuasive because the totality of the prior art makes the claimed invention obvious not Nicolaisen alone. Also see In re Keller and In re Merck & Co.

In response to applicant's argument that one of ordinary skill in the art would have been motivated to combine the teaching to produce a slow release form of Factor VII, is not found

persuasive because the motivation is no longer the reason for combining Wolf and Nicolaisen and Miller. "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR, 550 U.S. at ___, 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ."Id. at ___, 82 USPQ2d at 1396.

Claims 1, 24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf taken with Nicolaisen in further view of Miller as applied to claims 1, 2, 13-25, 29, 30, 32, 34, 35, and 41 above, and further in view of Amalfitano et al. (US 6,328,958).

Wolf taken with Nicolaisen and Miller do not specifically teach using an EF-1-alpha promoter in the composition.

However, at the time the invention was made, Amalfitano teaches a heterologous nucleotide sequence (e.g., clotting factor) operatively associated with a cytomegalovirus (CMV) major immediate-early promoter, an albumin promoter, an Elongation Factor 1-.alpha. (EF1-.alpha.) promoter, a P.gamma.K promoter, a MFG promoter, or a Rous sarcoma virus promoter. See columns 19-20.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wolf taken with Nicolaisen and Miller in further view of Amalfitano, namely to produce the composition comprising an EF1-alpha promoter. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently express Factor VII in a cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/24/07 have been fully considered but they are not persuasive because the arguments have already been addressed in the response to prior arguments directed to Wold taken with Nicolaisen.

Claims 1, 24, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf taken with Nicolaisen and Miller as applied to claims 1, 2, 13-25, 29, 30, 32, 34, 35, and 41 above, and further in view of Kochanek (US 5,981,225).

Wolf taken with Nicolaisen and Miller do not specifically teach using a skeletal muscle actin or muscle creatine kinase (MCK) promoter in the composition.

However, at the time the invention was made, the use of the MCK promoter will lead to tissue specific expression of a foreign gene (column 13).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Wolf taken with Nicolaisen and Miller in further view of Kochanek, namely to produce the composition comprising a skeletal muscle actin or muscle creatine kinase promoter. One of ordinary skill in the art would have been motivated to combine the teaching to selectively express Factor VII in a desired cell. See ***KSR v. Teleflex***.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/24/07 have been fully considered but they are not persuasive because the arguments have already been addressed in the response to prior arguments directed to Wold taken with Nicolaisen.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 13-23, 29-32, 34, 35, and 41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7,211,558 in view of Scaria et al. (US 20030229036). The claims of '558 teach a nucleic acid encoding a modified coagulation factor (Factor VIII) comprising a proteolytic cleavage site comprising RKRRKR. However, the claims from '558 do not specifically teach a Factor VII comprises the proteolytic cleavage site.

However, at the time the invention was made, Scaria teaches vector (AAV, retroviral, plasmid, and lentiviral) comprising a promoter operably linked to a nucleic acid encoding a modified Factor VII comprising a PACE/furin cleavage site replacing the activation cleavage site of Factor VII and a pharmaceutical acceptable carrier (pages 1-11). The vector encodes a modified version of Factor VII such that it leads to generation of (or can be converted to) activated Factor VII in vivo (page 3). Scaria teaches that activation of Factor VII to Factor VIIa involves proteolytic cleavage at a single bond between arginine 152 and isoleucine 153 (page 2) resulting in a heavy and light chain. Factor VII can be from any mammalian source, including human (page 4). The Factor VII can have one or more conservative amino acids (page 4).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the claims of '558 and Scaria, namely to produce a nucleic acid encoding a modified Factor VII comprising a proteolytic cleavage site comprising RKRRKR. One of ordinary skill in the art would have been motivated to combine to produce an active form of Factor VII.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635